REMARKS

Reconsideration is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 26-34 stand rejected over the alleged inherent teachings of Pouletty, et al. (U.S. Patent No. 5,837,247) in view of Breton, et al. under 35 U.S.C. § 103. For the numerous reasons outlined below, applicants respectfully request that the Examiner withdraw the rejection of the claims under 35 U.S.C. § 103.

Inherency

A. Inherency may not be the basis for a prima facie case of obviousness.

In the Advisory Action mailed July 28, 2004, the Examiner stated "Pouletty, et al. teach a method for increasing half-life of therapeutic peptides using non-denatured albumin, which inherently involves a step of analyzing the peptide blood component for resistance to peptidase degradation, as discussed by Breton, et al." (Advisory Action of July 28, 2004, page 2). The Examiner asserts that the combination of the inherent teachings of Pouletty, et al. combined with Breton, et al. render the pending claims obvious. Applicants respectfully assert that an obviousness rejection that relies on the inherent teaching of a reference is an improper application of the law.

The Examiner is respectfully reminded that it is well established that inherent teachings may not be relied upon in making a prima facie case of obviousness. There are several Federal Circuit opinions that are on point and support applicants' position that the Examiner is misapplying the law in putting forth an obviousness rejection based upon an inherent teaching. In *In re Rickaert*, the Federal Circuit reversed an obviousness rejection based on the combination of two prior art rejections, where one of the limitations was inherently taught by one of the references. *See In re Rickaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). The court held that a prima facie case of obviousness had not been established because "[t]hat which is inherent is not necessarily known.

Obviousness cannot be predicated on what is unknown. Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." *Id.* (citations omitted); *see also In re Spormann,* 150 USPQ 449, 452 (CCPA 1966). In a similar case, the court reversed an obviousness rejection based on the combination of two references, stating "a retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination. It is well established that in deciding that a novel combination would have been obvious, there must be supporting teaching in the prior art. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Newell*, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989). *See also* M.P.E.P. § 2141.02 ("obviousness cannot be predicated on what is unknown at the time the invention is made, even if inherency as a feature is later established.") Thus, a prima facie case of obviousness, based on an inherent teaching of Pouletty, et al. in view of Breton, et al., is an improper application of the law.

In light of this well settled law, applicants request that the Examiner withdraw the obviousness rejection.

B. The affirmative method steps of the present claims are not inherent in Pouletty et al.

Even assuming, *arguendo*, that the Examiner could put forward a proper prima facie case of obviousness by combining the inherent teachings of Pouletty, et al and Briton, et. al. such a rejection is improper because the affirmative method steps alleged to be inherently disclosed in Pouletty, et al. are simply not inherent in the teachings of Pouletty, et al.

It is well established that in order for a reference to anticipate a claimed invention when the reference is silent about the asserted inherent characteristic, the missing descriptive matter must be shown to be necessarily present in the thing described in the reference, and that it would be so recognized by the person of ordinary skill in the art. See Continental Can Co. v. Monsanto Co., 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). "Inherency may not be established by probabilities or possibilities," In re Oelrich, 212 USPQ 323, 326 (CCPA 1981), and "occasional results are not

inherent." Mehl-Biophile Int'l Corp. v. Milgraum, 52 USPQ2d 1303, 1306 (Fed. Cir. 1999). Examination procedures under the M.P.E.P. are in accordance with the case law on inherency, and describe an examiner's burden in making such a rejection as follows:

> In relying on the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.

M.P.E.P. § 2112 (emphasis in original).

The prima facie burden rests with the Examiner, not the Applicants.

The Examiner asserts that Pouletty, et al. inherently teaches a step of "analyzing the peptide blood component for resistance to peptide degradation." This is simply not true.

To be inherent, the step of "analyzing the peptide blood component for resistance to peptide degradation" must necessarily flow from Pouletty, et al. The teachings of Pouletty, et al. do not necessarily flow to performing this step. Pouletty, et al. teach the increased half life of a wide range of compounds of interest, most not subject to peptidase degradation, by binding the compounds to blood components. For example, Pouletty, et al. disclose the delivery of numerous agents which have an extended half life. Such agents may include sugars, particularly oligosaccharides. Such sugars are not subject to peptidase degradation because they are not peptides. However, the half life of these sugars are increased by the techniques of Pouletty, et al. In reading Pouletty, et al., one would speculate that the mechanisms of increasing the half life of sugars and peptides should be similar. If these mechanisms are similar, they cannot necessarily involve the same mechanisms of protecting a protein from peptidase degradation because the oligosaccharides are not peptides. More importantly, Pouletty, et al. does not disclose or suggest either inherently or otherwise analyzing the peptide blood component for resistance to peptide degradation.

The Examiner relies on the possibility that protection from peptidase degradation may occur under the Pouletty, et al. method. However, the fact that a certain result can be achieved only some

of the time is insufficient to establish inherency. *E.g.* In re Oelrich, 212 USPQ at 326; Mehl-Biophile Int'l Corp. v. Milgraum, 52 USPQ2d at 1306.

In sum, the Examiner's use of inherency as grounds for a prima facie obviousness rejection is incorrect. Furthermore, the methods step allegedly inherent in Pouletty et al. do not necessarily flow from the teachings of Pouletty, et al., as required, and are therefore not inherent. Applicants respectfully request that this ground for rejection be withdrawn.

Obviousness

Even assuming, *arguendo*, that the Examiner could legally put forward a proper obviousness rejection by the inherent teachings of a Pouletty, et al combined with Briton, et. al. and that the Pouletty, et al. reference inherently taught "analyzing the peptide blood component for resistance to peptide degradation," the Examiner has still failed to put forward a proper *prima facie* case of obviousness.

Examination procedures under the M.P.E.P. describe the Examiner's burden in establishing a prima facie case of obviousness:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

M.P.E.P. § 2142. Unless all three requirements are satisfied, the claimed invention is non-obvious.

A. The cited references do not provide the motivation or suggestion to combine their teachings.

The Examiner has stated that applicants have attacked the references individually but not in combination. Applicants respectfully disagree. For clarity, applicants provide the following.

First, the references, in combination, fail to provide the required motivation or suggestion to perform the presently claimed invention. A person of ordinary skill in the art would not be motivated to react to a blood component cited by Pouletty, et al. using the method illustrated by Breton et al. The combination of Pouletty, et al. and Breton, et al. does not provide any incentive to create a peptide-albumin conjugate consisting of a peptide between 3 and 50 amino acids and non-denatured albumin; nor do the references, in combination, suggest that such a conjugate could be analyzed and selected based on higher stability towards peptidase degradation.

B. The combined references establish an expectation of failure rather than success.

Second, the references, in combination, fail to establish a reasonable expectation of success. To the contrary, the combined teachings of Pouletty, et al. and Breton et al. would indicate to a person of ordinary skill in the art that success would be highly unlikely.

In the Office Action of April 7, 2004 at page 6, the Examiner indicated, in reference to the increased half-life of the Pouletty conjugates, "any increased half-life would necessarily involve an element of increased resistance to peptidase degradation." However, an increase in resistance to peptidase degradation is not taught by Pouletty, et al. Pouletty, et al. do not provide any indication or mention of increased peptidase degradation resistance from binding, *in vivo*, to blood components. The increased half-life of peptides taught by Pouletty, et al. could be a product of several metabolic mechanisms which affect a number of compounds, such potential mechanisms include: decreased elimination and clearance, decreased phagocytosis, and decreased cellular uptake. As discussed above, the teachings of Pouletty, et al. encompass a number of compounds: "The agent of interest may be varied widely, including naturally occurring compounds, synthetic compounds, and combinations thereof....Other compounds of interest, may be sugars...antibiotics, antihypertensive

agents, anti-coagulants, analgesics, hormones, chemotherapeutic agents, immunosuppressive or immunoregulatory agents...." (U.S. Patent No. 5,837,247). The majority of these agents are not subject to peptidase degradation; yet, as taught by Pouletty et al., all of these agents would enjoy an increase in half-life. For example, sugars are not peptides and therefore not subject to peptide degradation. Therefore, contrary to the Examiner's position, increasing half-life using the Pouletty, et al. method does not necessarily equate to protection from peptidase degradation. A person of ordinary skill would not consider increased resistance to peptidase degradation to be the mechanism of half-life increase in the Pouletty, et al. method because there are other non-peptide agents not subject to peptide degradation whose half life is increased.

Furthermore, Breton et al., only demonstrate peptidase degradation resistance, *ex vivo*, for a single, 411 amino acid precursor of a plasminogen activator when combined with a chemically denatured, non-native mutant of albumin. A person of ordinary skill would reasonably expect that peptidase degradation resistance is a function of the altered, denatured albumin described by Breton, et al.

Rather than having a reasonable expectation of success on combining the two references, a person of ordinary skill would reasonably expect that stability towards peptidase degradation necessarily requires conjugation to de-natured albumin, rather than the natural blood components of Pouletty, et al., and possibly only functions for larger peptides. Stated in other terms, a person of ordinary skill would reasonably expect failure rather than success and view the two teachings as mutually exclusive in their use, on the one hand, of natural blood components *in vivo* in comparison to the de-natured mutant serum albumin used *ex vivo* by the other. As such, Breton, et al. teaches away from the claimed invention.

C. The combined, cited references fail to teach or suggest the use of non-denatured albumin for increasing resistance to peptidase degradation.

Finally, the references, in combination, fail to teach or suggest all the claim limitations. Neither Pouletty et al. or Breton et al., separately or in combination, teach the analysis, and

subsequent selection, of peptide-non-denatured-albumin conjugates for stability towards peptidase degradation.

The Examiner stated in the Office Action of April 7, 2004, at page 6: "[T]he features upon which applicant relies (i.e., chemically modified, non-native albumin) are not recited in the rejected claim(s)." In response to the Examiner's statements, now pending claims 26-34 cure this and specifically refer to non-denatured albumin. The references, in combination, do not teach the use of non-denatured albumin in a method for increasing resistance to peptidase degradation.

The Examiner stated "Breton et al. teach the natural function of albumin to protect peptides from peptidase degradation that is analyzed or measured in half-life." (Office Action of April 7, 2004, page 6). Quite the opposite, Breton et al. teach that denatured, mutant albumin has a protective function with regards to peptidase degradation. The albumin used by Breton et al. differs markedly from that used in the present invention in both the crucial secondary and tertiary structures, components that play a key role in peptide and protein activity. The teachings of Breton et al. are clear: natural albumin lacks the protective functionality and must be heavily modified to acquire such a protective function. Therefore, the required claim limitation of analyzing a conjugate consisting of a peptide from 3 to 50 amino acids long and non-denatured albumin for increased stability towards peptidase degradation is absent from the combined references.

The references, in combination, do not provide a *prima facie* case for obviousness. Pouletty, et al. and Breton et al. combined do not provide the requisite suggestion or motivation to combine. The combined references do not provide a person of ordinary skill in the art a reasonable expectation that a combination similar to the present invention would succeed. Finally, the references fail to teach the critical claim limitation of analyzing a non-denatured, peptide-albumin conjugate for stability towards peptidase degradation. The Examiner having failed to establish a prima facie case for obviousness, Applicants respectfully request that this ground for rejection be withdrawn.

Conclusion

In view of the claims and arguments herein, the pending claims are now in condition for allowance.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. **500862002300**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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